Brussels, 27 May 2022

COST 065/22

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action "GENERATION OF HUMAN INDUCED PLURIPOTENT STEM CELLS FROM HAPLO-SELECTED CORD BLOOD SAMPLES" (HAPLO-iPS) CA21151

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action GENERATION OF HUMAN INDUCED PLURIPOTENT STEM CELLS FROM HAPLO-SELECTED CORD BLOOD SAMPLES approved by the Committee of Senior Officials through written procedure on 27 May 2022.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA21151
GENERATION OF HUMAN INDUCED PLURIPOTENT STEM CELLS FROM HAPLO-SELECTED CORD BLOOD SAMPLES (HAPLO-iPS)

The COST Members through the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action, referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any document amending or replacing them.

The main aim and objective of the Action is to to create a collaborative network to provide a framework for hiPSC generation of hiPSC homozygous for frequent HLA haplotypes, compatible with a significant percentage of the population to be used for cell therapy and to create a data collection system (REGISTRY) for such lines. This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

OVERVIEW

Summary
HAPLO-iPS aims to create a collaborative network to provide a framework for hiPSC generation of hiPSC homozygous for frequent HLA haplotypes, compatible with a significant percentage of the population to be used for cell therapy clinical trials and to create a data collection system (REGISTRY) for such lines.

HAPLO-iPS will establish an European-based excellence network on hiPSC-derived cell-based medicines that not only will boost the state-of-the-art of this research field if not will also contribute to Europe worldleadership through the medical, scientific, economic, and social development of Europe and strengthening
Europe's competitiveness capacities. This network includes all the relevant stakeholders: hiPSC generation/banking centres, CB banks that will supply cord blood units; manufacturing centres (GMP complying), immunology experts, chemistry and manufacturing controls, regulatory bodies, National Agencies, and ethics experts. The challenge will be approached essentially by networking with all the stakeholders involved sharing knowledge, standardizing methodology and developing an educational training programme for researchers.

HAPLO-iPS is also promoting the participation of researchers from less research-intensive countries as a significant percentage of the members are from ITC countries. ITC participants will have access to research facilities, training courses, mentoring of ITC young researchers and will participate spreading excellence and widening participation programme. Furthermore, Key leadership positions in the Action Management are reserved to COST ITC.

Overall, this proposal will pioneer new approaches that will foster the progress of a haplo-selected hiPS generation of therapeutics by the development, implementation and exploitation of a registry with all the information for the benefit of patients.

Areas of Expertise Relevant for the Action	**Keywords**
● Biological sciences: Stem cell biology	● human induced Pluripotent Stem Cells (hiPSC) ● Cord Blood samples ● HLA homozygous haplotypes

Specific Objectives
To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination
● The development of a common understanding of the /HLA / CB sample selection procedure KPI
● The coordination of information seeking, tracing, collection and data curation of the selected samples KPI: Guidelines for sample selection
● Comparison and optimisation of methodologies for the generation of hiPSC suitable for the manufacture of therapeutic products, including machine learning based monitoring, automation and scaling. KPI SOPs for Reprogramming methodologies
● Identification of optimal systems for safety-assured and reliable cell therapies to promote standardisation

of hiPSC characterisation for basic and clinical researchers and regulators. KPI SOPs for Characterisation of pluripotency.
● Establish core requirements for evaluation of suitability of hiPSC in terms of differentiation potential and elimination of reprogramming vectors. KPI SOPs for Differentiation
● Bring together expertise in genetic stability and tumorigenicity testing for evaluation of best current scientific practice in cell safety testing KPI SOPs for Safety standards
● Establish a consensus approach to identification and testing for the wider range of acute and emerging infectious diseases beyond the viral infections tested for in transplantation KPI SOPs for Safety standards
● Development of a data resource and access platform for available hiPSC for the manufacture of therapeutic products based on the existing hPSCreg. KPI Database in hPSCReg
Definition of hiPSC and linkage to existing repositories; provision of a source overview for donor material via a single portal KPI Haplo hiPSC Portal
● Establishment of ethical core documents for donation and clinical use of CB-derived hiPSC, landscaping of the regulatory and licensing environment and development of navigation support KPI Document for Consent Form and Information Sheet
● Medico-economic issues: To develop a sustainability model. KPI: External report.

Capacity Building
● Promoting knowledge exchange around the generation of hiPSC suitable for the manufacture of cell therapy products, considering the opportunities currently available and identifying future tools and approaches that could add value, and making recommendations for future development.
● Promoting networking among the different stakeholders involved to identify key issues and potential solutions in production of suitable cell lines. Multi- and interdisciplinary approach: bridging basic scientists and clinicians working in reprogramming methodologies and cell therapy, standards organisations, regulators and ethics experts.
● Acting as a stakeholder platform for the application of cell therapy with hiPSC derivatives and seeking added value of the network for other areas of cell-based medicines and therapies
● Provision of training and educational programs and exchange for young scientists and clinicians between the member states.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. SOUNDNESS OF THE CHALLENGE

1.1.1. DESCRIPTION OF THE STATE OF THE ART

There is a critical need worldwide for tissue for transplantation in patients with organ failure and an increasing impact of degenerative age-related human diseases for which there are very limited or no treatments available (Saidi and Kenari, 2014). Cell therapy can constitute a future alternative to organ transplantation and for the treatment of degenerative diseases (such as macular degeneration, Parkinson's disease, heart failure, type I diabetes, or spinal cord injuries, to name a few) (Kobold et al, 2020). The generation of human induced pluripotent stem cells (hiPSC) from somatic cells offers a unique opportunity to obtain a virtually unlimited supply of a broad spectrum of specialized cells (Takahasi et al., 2007; Yu et al., 2007). hiPSC derivatives have a great potential for cell replacement therapy even though the clinical relevance of such treatments is still to be clinically realized in the form of licensed cell-based medicines (CBM). There are some registries of available hPSC. The most prominent is the European human Pluripotent Stem Cell Registry hPSCreg (https://hpscreg.eu/) that was created as a registry of European lines but now it involves hPSC lines from over the world. Although individual approaches for using hiPSCs for therapeutic applications already exist (reviewed in Kobold et al, 2020) and also for setting up the first haplo-banks throughout Europe, these initiatives are not yet working as a co-ordinated community (described in S & T Excellence, Description of the State of the Art) and only have the capacity to provide cell lines for a limited number of common HLA haplotypes. To date these approaches, that still are at the proof-of-principle stage, will at best cover only a limited percentage of the population in need. With their limited resources, they result in a social-economic imbalance and even exclusion of certain population groups from future medical possibilities. Furthermore, there are key scientific and regulatory discussions yet to be resolved to achieve a European consensus on essential issues that must be tackled to progress such haplo-registry/bank resources to a clinical reality. The use of patient's cells for the generation of hiPSC and subsequent differentiation to the desired cell type for treatment ensures immunological compatibility and minimizes the risk of rejection. However, the time and cost necessary for the production of customized hiPSC lines and their derivatives that would be suitable for use in humans is prohibitively high. For a large scale therapeutic landscape, immune-HLA matched IPSC lines suitable for a wide variety of HLA genotypes would be valuable for significant numbers of patients.

An alternative to the use of patient-specific hiPSC would be a hiPSC collection from allogeneic healthy donors that could be expanded and differentiated to treat different patients. To reduce the risk of immune rejection, this allogeneic hiPSC collection should comprise lines with sufficiently diverse and compatible homozygous HLA haplotypes to ensure maximum possible population coverage. Manufacturing of scalable unique cell standardized final products from haplo-selected hiPSCs suitable for various types of diseases and multiple clinical indications, should in addition reduce the cost of the final products and patient immune-suppression. Cell derivatives from HLA-matched hiPSC banks will allow delivery of off-the-shelf cell therapy products, easily accessible for critical acute or subacute diseases and for new emergent diseases such as the current pandemic SARS-2-induced inflammatory disorders.

This idea was already proposed by Bradley et al. (2002) and Taylor et al. (2005) for embryonic stem cells (hESC). hiPSC technology facilitates the prospective selection of interesting donors based on their particular HLA haplotypes (Nakatsuji et al., 2008).

The selection of homozygous donors for common HLA haplotypes for the generation of hiPSC would facilitate compatibility with potential recipients. Nakatsuji et al. calculated that 30 carefully selected hiPSC lines would provide coverage to 82.2% of the Japanese population coinciding in the 3 loci (HLA-A, HLA-B and HLA-DR), and 90.7% of the population would be covered with 50 hiPSC lines. However, identifying these 50 potential donors would necessitate studying the HLA system of 24,000 individuals. Okita et al. (2011) calculated that 140 homozygous donors for HLA haplotypes would cover 90% of the Japanese population, requiring the screening of 160,000 potential donors.

Similarly, Gourraud et al. (2012) calculated that 26,000 donors of European-American ancestry and 110,000 donors of African American ancestry would need to be screened to obtain hiPSC representing the 20 most frequent HLA haplotypes, and that these lines would provide coverage to 50% and 22% of these populations, respectively. All this confirms that relatively few donors, but very carefully selected, would allow the generation of hiPSC lines with a strong potential for clinical utility. Similar calculations have been established for Korean population in comparison with China, Japan and the West. (Lee et al., 2018). Alvarez-Palomo et al., (2021) calculated that 10 cord blood units from homozygous donors stored in the Spanish cord blood banks can provide matching for 28,23% of the Spanish population. The collaboration of multiple centres worldwide would be necessary to perform the screening and identifying individuals among the large number of potential donors (Taylor et al., 2012).

One feasible possibility is to prospectively search for potential donors in registries/banks of bone marrow and cord blood (CB), since these donations are already typed for elements of the HLA system. Several reasons make CB cells the cell type of choice to generate homozygous HLA haplotype hiPSC collections for clinical translation: i) there is no risk for either the mother or the new-born at collection; ii) cord blood units, preserved in cord blood banks, are already HLA typed, which facilitates donor screening; iii) cells in the cord blood are less likely to have accumulated genetic or epigenetic risks compared to adult and differentiated cells; and iv) hiPSC generation methodology with CB samples is well established (Giorgetti et al, 2009; Lee et al., 2018). The use of CB-hiPSC as an alternative to the use of patient-specific hiPSC would minimize the time and cost necessary for the production of customized hiPSC and their derivatives. Moreover, although CB samples are designated for clinical application for haematological pathologies, many CB banks keep surplus samples sufficient to generate hiPSC lines and CB samples with an insufficient number of haematological progenitors not suitable for transplantation might also be used. Methodology for GMP-grade CD34+ selection from HLA-homozygous cord blood units has been reported (Liedtke et al., 2020).

In a recent report, Lee et al. (2018) describes the generation of hiPSC lines with the 10 most frequent HLA-homozygous haplotypes, which can match 41.07% of the Korean population. Comparative HLA analysis indicates that the lines are relevant to other Asian populations, such as Japan, with some limited utility in ethnically diverse populations, such as the UK. Similarly, Rim et al., (2018) report the generation of 13 homozygous GMP-grade hiPSC lines from blood and cord blood cells with selected homozygous HLA types from the Catholic Hematopoietic Stem Cell Bank of Korea.

The World Marrow Donor Association (WMDA) estimates 256.006 Cord Blood Units (CBU) preserved in the cord blood banks in Europe and 798.372 units in the world (https://statistics.wmda.info/). Bone marrow registries represent an alternative to CB banks as potential providers of samples for hiPSC generation, but both the availability, lower invasiveness and the easy access to samples in the latter are

obvious advantages to be considered. There are 37.346.669 bone marrow donors registered in the WMDA registry (https://statistics.wmda.info/).

Another option to be considered to get hiPSC compatible with a significant percentage of the population is the use of genetic modification techniques in hiPSC or hESC to knock-out or down-regulate HLA genes to generate “universal” donor cells. Xu et al, 2019 described two genome-editing strategies for making immunocompatible donor hiPSCs. First, they generated HLA pseudo-homozygous hiPSCs with allele-specific editing of HLA heterozygous hiPSCs. Second, they generated HLA-C-retained hiPSCs by disrupting both HLA-A and -B alleles to suppress the NK cell response while maintaining antigen presentation. HLA-C-retained hiPSCs could evade T cells and NK cells in vitro and in vivo. The authors estimated that 12 lines of HLA-C-retained hiPSCs combined with HLA-class II knockout are immunologically compatible with >90% of the world’s population, greatly facilitating hiPSC-based regenerative medicine applications. Other publications also report encouraging results using similar or RNA silencing techniques as well as cell-based immunomodulation strategies genetic ablation of HLA molecules from hiPSC combined with gene transduction of several immunoregulatory molecules (Petrus-Reuer et al, 2020; Suzuki et la, 2020). These ‘universal’ hypo-immunogenic strategies could be valuable for rare haplotype cells, and in relevant clinical applications such as hematopoietic cell transplantation, where HLA mismatches profoundly affect engraftment, or in autoimmune diseases, where autoantigen presentation would cause side effects. Non-HLA minor histocompatibility antigens from Y chromosome genes, and SNPs profiling should also be taken in account. However, genome editing could induce a risk of off-target modifications that must be extensively controlled, and such modifications can enhance the complexity of safety evaluation and regulatory delay. These both non-exclusive models will be enriched by variant models, and innovative strategies will evolve as a step towards complete immune-matched hiPSC lines with fully personalized therapy

Few commercialized allogeneic clinical-grade hiPSC lines are currently available from private companies (Fuji-CDI, in Wisconsin USA from the 5 most common HLA types matching to 35% of US population), with non-exclusive license fee and restriction rights to develop and commercialize a product. Very few allogeneic hiPSC lines for cell therapy are provided by public research organizations such the NIH through RUCDR Infinite Biologics, Korea HLA-Typed iPSC Banking (KHIB), and the Centre for iPS Cell Research and Application (CiRA). CiRA has generated a total of 27 hiPS cell lines made from 7 donors (4 peripheral blood and 3 cord blood) who are homozygous for 4 the most frequent HLA types in Japan. These lines cover approximately 40% of the Japanese population. Kim et al., (2021) recently reported 22 GMP- compliant homozygous HLA-type iPSC lines, which cover HLA haplo-type matching for 51% of the Korean population The different lines give versatility in HLA typing and differentiation capacity for the treatment of different diseases. Some of these cell lines have already been used in hiPSC cell-based clinical cell therapies. A European hiPSC collection to manufacture cell therapy products needs to be developed within a global organization to face emerging scientific medical and industrial needs.

Cell lines for use in human therapy need to be established in GMP conditions in facilities with a relevant product manufacturing license under strict quality assurance. These lines must also be generated with all ethical and legal requirements (Jha et al., 2021). Use of hiPSC lines as a starting material for the manufacture of cell therapy products requires demonstration of comparability of lines derived from different individuals and in different facilities. This needs agreement on the quality attributes of such lines and the assays that should be used (Sullivan et al., 2018; O’Shea et al., 2020; Abranches et al., 2020).

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

The aim of this COST Action is to create a collaborative network to provide a framework for hiPSC generation of hiPSC homozygous for frequent HLA haplotypes, compatible with a significant percentage of the population to be used for cell therapy and to create a data collection system (REGISTRY) for such lines.

The size of this challenge becomes clear with some numbers. It is estimated that 405 theoretical HLA homozygous combinations are sufficient to cover 100% of the UK Caucasian population - based on a sample of 10.000 real persons to be matched. The hurdle to be overcome is that of these 405, only 236 existed in a pool of 17 million registered donors. Therefore, far more than 17 million need to be screened to find all required combinations. Currently, about 22 million HLA-mapped donors are registered worldwide.

One aspect of the HAPLO-iPS COST Action is therefore to elucidate strategies to identify the best possible approach to access donor pools. HAPLO-iPS will develop a strategic framework using CB sample donations as a source as these provide the most accessible source for hiPSC generation. The framework can be expanded to other HLA typed sources such as bone marrow registries and HLA modified cells, as described above.

This network includes all the relevant stakeholders: hiPSC generation and banking centres, CB banks that will supply cord blood units, manufacturing centres complying with Good Manufacturing Practice (GMPs) and chemistry and manufacturing controls (CMCs) to produce stem cell derivatives for cell therapy (ATMP experts), clinicians and clinical centres involved or aiming to get involved in cell therapy using hiPSC derivatives, and regulators such as National Agencies that supervise compliance with the regulations in the different countries. Ethics experts for the correct handling of samples and adequate data confidentiality and sharing sample procedures are also included in the network. Immunology experts have also been considered in the Action to ensure an optimal selection of the CB samples. The overall aims of this Action will also benefit significantly from broader international interactions that will be facilitated through established international stem cell networks.

Even so, it must be considered that producing hiPSC that are suitable for manufacture of therapeutic products involves more than quality standards and key cell line characteristics must also be addressed for their impact on safety and efficacy of the final products. The use of hiPSC derivatives for cell therapy requires special attention not only to quality control processes but also with respect to assessment of the differentiation properties, tumorigenicity and genome integrity as well as guidelines for ethics and regulatory advice/contacts (such as license landscape), registration and ‘look up’ systems (available manufacturing capacities), and strategic road-map including other possible source materials. In addition, the utility of haplo-banks and registries of hiPSC lines to make a single product type will require special attention to establish appropriate comparability studies to assure that multiple cell lines can generate an equivalent product.

1.2. PROGRESS BEYOND THE STATE OF THE ART

1.2.1. APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE OF THE ART

Networking, with all the stakeholders involved and in different ways, will provide our main approach to the challenge. By forming interdisciplinary but connected Working Groups (WG) within the main network

structure, we will focus complementary expertise and knowledge where it is needed, mainly on the drafting of guidelines and best practice papers as well as in putting in place a registration tool for the cell lines generated. As an innovative approach, this network will create a framework for the evaluation of the quality and safety of the available CB resources for the development of hiPSC-derived cell-based medicines. This network will be structured in 7 WG:

WG	WG Title	Stakeholders involved
1	**Sample selection**	CB banks, hiPSC generators,
2	**hiPSC production**	hiPSC generators, cell therapy products manufacturers
3	**Quality control, Biobanking and Registration o cell lines**	hiPSC generators, cell therapy products manufacturers, biobanks, regulatory bodies, hPSCreg
4	**Safety and Regulation**	Immunologists, Regulatory bodies, cell therapy products manufacturers
5	**Management, data handling and Ethics**	Management team, CB banks, geneticists, experts in data handling and protection, ethical experts
6	**Training and dissemination**	CB banks, hiPSC generators, immunologists, experts in data handling, website developers
7	**Clinical application**	Regulatory bodies, cell therapy products manufacturers, clinical researchers, immunologists, hiPSCreg

Knowledge sharing is a core element of the Action, and it is essential in tackling the process of standardisation of methodology as this is a vital part of the work proposed. Even though hiPSC generation methodology is well established and standardised, the efficiency is still low with certain methodologies and types of cells of origin, especially in clinical grade conditions. The Action intends to establish optimised protocols and methodology for an efficient, safe, standardised and affordable generation of hiPSC with less variability and more suitable for the manufacture of therapeutic products. Dissemination of standardised methodology constitutes an essential aim of the Action. There are already some initiatives in place developing standards in the cell-based medicines field. Significant progress has been made in building consensus of mandatory and informative quality control for hiPSC lines and suitable quality and safety standards for hiPSC (Sullivan et a., 2018; Jo et al., 2020) for use in cell therapy. The Action could bring significant benefit to translate these into the hiPSC research and therapy community, which needs specific requirements to be adopted for quality and risk assessment and new standards to be developed for hiPSC generation and manufacturing. Essential for achieving global consensus on such standards, a set of reference materials need to be developed and defined within the Action, with an external quality assurance scheme to facilitate comparability of analytics across different Centres.

This Action will establish this innovative strategy to avoid unnecessary duplication in the generation of hiPSC lines of the same haplotypes in different centres and countries, thus saving time and optimizing valuable resources. The innovative approach will also include putting in place a central database for accessing comprehensive and detailed information to assess suitability of available hiPSC lines. Already existing hPSC registries such as the human Pluripotent Stem Cell registry (hPSCreg) (https://hpscreg.eu/) will be used for the registration of the cell lines generated.

The HAPLO-iPS educational training programme will provide another key benefit for researchers, clinicians and students in the cell therapy field, offering expert training in the key steps of donor selection, safe reprogramming, quality control and risk assessment for efficient and safe translation from CB

samples to hiPSC-based therapy (theory and hands-on training). These will include critical issues in assuring regulatory acceptability for the quality and safety of iPSC for therapy. Furthermore, the network will develop best practice guidelines for the complex issues of ethics and data management and how these would apply to future hiPSC HAPLO-Banks and Registries. Common standards for hiPSC lines for cell therapy used across international regulatory agencies are crucial for accepting effective and safe cell therapies across international boundaries. Opportunities for direct lab exchanges will be encouraged through an exchange system to enable trainees to request support and introductions.

1.2.2. OBJECTIVES

1.2.2.1 Research Coordination Objectives

The Action objectives will cover four main areas:

A. Source material screening, selection, collection and tracing
   - The development of a common understanding of the /HLA / CB sample selection procedure KPI: Report on the common understanding
   - The coordination of information seeking, tracing, collection and data curation of the selected samples KPI: Guidelines for sample selection

B. Generation of hiPSC, characterization and risk assessment
   - Comparison and optimisation of methodologies for the generation of hiPSC suitable for the manufacture of therapeutic products, including machine learning based monitoring, automation and scaling. KPI SOPs for Reprogramming methodologies
   - Identification of optimal systems for safety-assured and reliable cell therapies to promote standardisation of hiPSC characterisation for basic and clinical researchers and regulators. KPI SOPs for Characterisation of pluripotency.
   - Establish core requirements for evaluation of suitability of hiPSC in terms of differentiation potential and elimination of reprogramming vectors. KPI SOPs for Differentiation
   - Bring together expertise in genetic stability and tumorigenicity testing for evaluation of best current scientific practice in cell safety testing KPI SOPs for Safety standards
   - Establish a consensus approach to identification and testing for the wider range of acute and emerging infectious diseases beyond the viral infections tested for in transplantation KPI SOPs for Safety standards

C. Information management and access to iPSC for clinical use
   - Development of a data resource and access platform for available hiPSC for the manufacture of therapeutic products based on the existing hPSCreg. KPI Database in hPSCReg.
     Definition of hiPSC and linkage to existing repositories; provision of a source overview for donor material via a single portal KPI Haplo hiPSC Portal

D. Ethics, regulation and economics
   - Establishment of ethical core documents for donation and clinical use of CB-derived hiPSC, landscaping of the regulatory and licensing environment and development of navigation support KPI Document for Consent Form and Information Sheet
   - Medico-economic issues: To develop a sustainability model. KPI: External report.

1.2.2.2 Capacity-building Objectives

- Promoting knowledge exchange around the generation of hiPSC suitable for the manufacture of cell therapy products, considering the opportunities currently available and identifying future tools and approaches that could add value, and making recommendations for future development.

- Promoting networking among the different stakeholders involved to identify key issues and potential solutions in production of suitable cell lines. Multi- and interdisciplinary approach: bridging basic scientists and clinicians working in reprogramming methodologies and cell therapy, standards organisations, regulators and ethics experts.
- Acting as a stakeholder platform for the application of cell therapy with hiPSC derivatives and seeking added value of the network for other areas of cell-based medicines and therapies.
- Provision of training and educational programs and exchange for young scientists and clinicians between the member states.

2. NETWORKING EXCELLENCE

2.1. ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1. ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

The aim of this COST Action is to set the basis for an inclusive approach, making stem cell therapies accessible and affordable for the broadest possible EU population in need. This will be achieved by considering the broad range of haplotypes needed to serve that community. The challenges presented by this Action require an international approach rather than a national or local one, given the magnitude and complexity of the proposed goals, the rarity of individuals with homozygous HLA haplotypes and the diversity of skills and resources required. The Action will consider the pluralistic nature across Europe on the ethical, legal and socioeconomic levels and the different stages of preclinical and clinical advances. The problem to be solved does not only affect a local or national community, not even a European one, instead it is a global concern for those working in the field.

Therefore, the time is ripe to combine the current efforts in one place, to set up a fully co-ordinated and state-of-the-art European haplo-registry from which to do the groundwork for future patient matched cell-based medicines. Necessary technologies are already described and the first hiPSC-based clinical trial in Europe is progressing (Cynata, UK) and others are moving forward worldwide (Kobold et al., 2020). Putting in place an EU haplo-registry will ensure strict data and procedural standards and harmonisation of the procedures used in the different centres involved throughout Europe, together with the definition of the required rigorous standards and regulatory acceptability regarding cell quality and safety. Comparability of the efficiency and safety of different hiPSC lines for therapeutic applications will also be essential. Legal and ethical issues will have to be aligned throughout the different European countries and decentralised GMP manufacturing centres and biobanking hubs will also have to be established with a smoothly working logistic network.

Furthermore, to reach the highest quality standards, traceability and automation solutions, all with effective standardisation measures in place must be proactively developed. This is crucial at all stages of cell production, characterisation and biobanking. However, hiPSC biobanking procedures are currently being developed largely within individual projects for GMP manufacture of cell-based products and the nature of the haplo-banking challenge means there are huge benefits to be realised from greater co-ordination between device developers, current users, future product developers and regulators at national, European and international levels.

A sophisticated combination of decentralised and centralised facilities for cell production, quality control and distribution is likely to be needed to serve the broad range of hiPSC cell-based medicines under

development. This will involve an extended quality control and auditing process to assure the same baseline for quality and safety in all participating resource centres throughout Europe. The HAPLO-iPS network already has a wide geographical distribution among the COST countries in order to achieve this and it is well placed to coordinate with broader international haplo-banking activity in Asia and the USA to further increase impact in this regard.

Biobanking and Quality Control are key stages to assure traceability and reliable testing data. This results in a robust pathway to clinical products to ensure safety assurance and reduced financial risk for product developers and their investors which has been evaluated in the major EC-funded iPSC biobanking project European Bank for induced pluripotent stem cells (EBiSC) (www.ebisc.org) (O'Shea et al, 2020).

Another essential part in the process is to define quality and safety standards in the methodologies used for the generation and characterisation of the cell lines as well as for the differentiation protocols to be used. By ensuring the active participation of clinicians and clinical centres that are already involved in or that would like to develop cell therapy products from hiPSC, we can guarantee the critical mass of S& T excellence necessary to ensure maximum quality and safety. HAPLO-iPS will also monitor clinical trials (CT) performed with hiPS derivatives.

Regulation, Ethics and Intellectual Property issues are also key considerations to help assure acceptability and effective mitigation of risks of using hiPSC haplo-registries/banks as sources for cell-based advanced cell-based medicines. WG5 will be in charge of take care of these issues.

Overall, HAPLO-iPS will add value to existing efforts at both the European and International level because it has all the prerequisites to provide a sustainable solution to avoid faulted workflow design and fragmented implementation of hiPSC derived products for cell therapy. HAPLO-iPS brings together an unprecedented pool of experts from Cord Blood banks, Reprogramming centres, Companies, clinicians, Regulators and Ethics experts in the relevant science domains. Furthermore, this COST Action aims to update and educate the researchers in the concepts and technologies necessary to further advance this field to deliver a cohort of consistently trained scientists and clinicians fit to engage in effective translational research and the development of future cell-based medicines. Overall, this Action will pioneer new approaches that will foster the progress of a haplo-selected hIPS generation for cell therapy by the development, implementation and exploitation of a registry including CT with hiPSC derivatives with all the information for the benefit of patients.

2.2. ADDED VALUE OF NETWORKING IN IMPACT

2.2.1. SECURING THE CRITICAL MASS AND EXPERTISE

The uptake of hiPSC generation to manufacture cell therapy products requires interdisciplinary and intersectorial collaboration to advance implementation. This COST Action unites lead basic l researchers, clinicians, regulators and industry together in a fully coordinated approach to facilitate and accelerate research towards hiPSC-derived products from bench to bedside. The knowledge and expertise required to achieve the defined objectives is accounted for by a cross-cutting and inclusive network of stakeholders combining their expertise from different areas such as Cord Blood Banks, Reprogramming Centres, Biobanking and Registry experts, clinical settings as well as ethicists, International Partner Countries and European RTD Organisations. Furthermore, the involvement of senior researchers actively driving research in the specific research area for a number of years, will increase the level of expertise in HAPLO-iPS. The balance provided by participating experts from the

different areas offers a unique approach to explore and drive opportunities for coordinated translational research through excellence in science and technology, knowledge transfer and also yields a high level of intrinsic motivation. Furthermore, the large network coverage at the time of submission (16 countries, and 29 proposers) including investigators, clinicians, regulators, ethicists and representatives from companies will secure the critical mass and diversity of input required for the implementation of the aims of this Action.

The network has expertise in the fields of cord blood registries and banks, the generation of hiPSC intended for clinical use and their regulatory issues, data management and training. These will be combined with experience in other complementary areas such as HLA genetics and hiPSC manufacturing, quality and risk assessment. Taken together, the network provides a powerful body of experienced researchers and clinicians and European experts in the field of stem cells and regenerative medicine in order to address the aims and the challenges of the Action, namely the standardisation of all processes involved in the generation of hiPSC for the manufacture of cell therapy products and the creation of a registry for cell line data collection.

The expertise and the involvement of the participants of HAPLO-iPS guarantees optimal input in all the WGs as well as bringing the aims and missions of the Action to realisation (see also section 2.2.2, which looks at stakeholder input). HAPLO-iPS also maintains the COST Excellence and Inclusiveness Policy with regards to developing researchers that are new to the field and also to assuring gender balance and other aspects of diversity are met. The biographical distribution assures opportunities for collaboration between professionals from different disciplines of the different European countries. This will promote progress on the aims of the Action, while also complying with the COST Policy to support the integration of scientific communities and participants from COST Inclusiveness Target Countries.

2.2.2. INVOLVEMENT OF STAKEHOLDERS

A multidisciplinary team of experts will be part of the Action organised in seven Working Groups. Cord Blood Banks (CBB) receive, process, store, quality control and distribute the umbilical cord blood samples. CBB make sure that samples are obtained properly typed and preserved allowing their traceability and screening and for clinical application are accredited under the European Union Tissues and Cells Directive (Immuno Polymorphism Database: https://www.ebi.ac.uk/ipd/imgt/hla/stats.html). Role: involved in the selection of adequate samples and the standardisation of minimum acceptance criteria for sample/donor selection. (WG1 and 6).

hiPSC generation and banking centres have as their main objective the generation of hiPSC collections, including the derivation, characterization, banking and registration of such lines. Role: in charge of standardization and harmonization of the current protocols and quality controls (including vector clearance, expression of pluripotent stem cell associated markers, pluripotency assessment, genome integrity and genetic risks, short tandem repeat assays (STR) and other authentication assays), improving the efficiency and avoiding duplication and redundant generation of hiPSC lines. They will also be involved in regulatory and specialized training through workshops and short-term scientific missions (STSM). (WG1, 2, 3 and 6).

Manufacturing centres are focused on development and manufacturing of stem cell for cell-based medicines. Role: with their expertise in GMP, they will be key actors for the future-proofing and establishment of characterization and quality control guidelines in stem cell production. WG2, 4 and 7).

Clinicians and clinical centres working in stem cell based therapies are in charge of the delivery of such products to the patients. Role: Their input in the production of clinical grade hiPSC is essential to allow safe and efficient stem cell based derivatives for use in Regenerative Medicine (WG7).

Regulatory Bodies, Standards Institutes and Ethics experts. Regulatory agencies and Standards Institutes will assess the compliance of the Action outputs with the regulations for the EU and specific views on matters such as facility inspection in the different countries, acceptability for the quality and safety of the products and the correct handling of the data. Regulatory Agencies and Standards Institute are involved in HAPLO-iPS COST Action. Ethics experts' involvement is also essential and International Ethics advisors will also be contacted during the Action development (Hervé Chneiweiss, Chairman, Ethics Committee INSERM, France, Rosario Isasi, hPSCreg ethics advisor and professor at Miami University USA). (WG3, 4, 5 and 7) Role: Developing of a roadmap and guide through the ethical and legal landscape of iPSC generation and use, including informed consent, data protection, license and patent landscape if needed.

Patient associations and patient organizations will be contacted after the Action is initiated and will be kept informed through the dissemination activities carried out. Role: to provide patients and the general public with the most up to date knowledge of the haplo-banking science and the Action registry (inclusion and visibility). (WG6 and 7).

Biotechnological and pharmaceutical companies have the expertise in development and manufacturing of cell-based medicines. Role: participate in the meetings and events of the Action in order to work on the innovative collaborative projects for the development of advanced therapies (WG2, 4 and 7).

2.2.3. MUTUAL BENEFITS OF THE INVOLVEMENT OF SECONDARY PROPOSERS FROM NEAR NEIGHBOUR OR INTERNATIONAL PARTNER COUNTRIES OR INTERNATIONAL ORGANISATIONS

HAPLO-iPS will invite and promote the inclusion of International Partner Countries during the implementation to allow harmonisation at international level (WG 2,3,4 and 5). The participant will benefit from HAPLO-iPS activities and HAPLO-iPS will benefit from the participant´s interdisciplinary knowledge of research on stem cell generation for clinical application.

3. IMPACT

3.1. IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAKTHROUGHS

3.1.1. SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

This COST Action has a huge potential impact at multiple levels as its ultimate goal is to utilise the power of innovative stem cell technology to provide every European citizen with a safety-assured, perfectly characterised and immunologically matched stem cell line. This will allow much wider access for European patients to treatment with future cell therapies and regenerative medicine without a long-

lasting or even unsuccessful search for compatible cell donors and the need for significant immunosuppression of recipient patients.

Short term impact

- Establishment of a registry of stocks of cord blood samples held in centres with suitable procurement, record keeping and HLA data to be accessible in European countries.
- Establishment of an interdisciplinary pan-European network of stakeholders that develops, assesses and works on the standardization of hiPSC homozygous generation for frequent HLA haplotypes suitable for the manufacture of cell therapy products.
- Establishment of a registry for haplo-selected hiPSC data.
- Identification of the state of the art of the current scientific best practice consensus in safety and quality assessment of hiPSC derivatives for cell therapy.
- Establishment of the most appropriate standards and a quality framework to enable individual centres to create and utilise cells generated in the network with greater confidence and lower risk.
- Engagement of training scientists in a highly multidisciplinary environment (e.g. by offering STSMs at SMEs, regulators or labs of experienced investigators in other countries).
- Raising of public awareness through the dissemination of implementation strategies for healthcare professionals, patients, decision makers and SMEs across Europe and the world, by means of development of several activities and channels (like meetings, training schools, scientific publications, outreach activities, registry).
- Analysis of ethical, legal and social implications of the production of stem cells for use in cell therapy.

Long term impact

- Technological impact: The generation of an efficient model that is acceptable to regulators, for taking forward multiple cell lines for single product types and thus rendering the haplo-registry principle financially viable, will accelerate technological innovation in the developing hPSC-manufacturing community. Moreover, the delivery of enhanced and regulatory-reviewed quality control and safety testing regimes and protocols will increase awareness about this technology worldwide.
- Clinical impact: patient-tailored products derived from HLA-matched starting materials (hiPSCs) will reduce the need for the generation of specific hiPSC for each patient and reduce the need for immunosuppression after cell therapy. Ultimately, this could lead to fewer medical complications, hospitalizations, lower mortality rates and better quality of life after the application of hiPSC derived cell therapy.
- Economic impact: Availability of improved quality cell line repositories will enhance the quality and safety of hiPSC products and reduce financial risk for the very expensive manufacturing and clinical trial process. On the other hand, the reduced immunosuppression and patient follow-up and management costs will have a significant impact in healthcare systems, especially in ITC countries.

Social impact: This technology will facilitate access to advanced cell-based medicines to the widest range of patients and the provision for currently unmet clinical need particularly in degenerative disease. Moreover, the COST Action will provide a cohort of trained scientists with key knowledge in translating stem cell technology to therapeutic application.

Innovation potential

By achieving the proposed goals, the impact will be high both within its own population now able to access future hPSC-based medicines and for EU therapeutic products worldwide. The proposed registries for biologicals (HLA-defined hiPSC lines, genetically engineered lines, protocols, annotated data, production data, etc.) and for medical infrastructures (GMP production facilities) will provide an innovative approach at the European level, providing an attractive ecosystem for (bio-) medical start-ups and Big Pharma to develop new therapies in the field of Advanced Therapy Medicinal products (ATMP). The consequences will be disruptive, as business models of standard pharma products (one development, multiple recipients) can be transferred to ATMPs. The broadest range of citizens of the European Union will have accelerated and (biologically) preferred access to new therapies. Every Citizen will feel the difference, as will the European research area and economy.

3.2. MEASURES TO MAXIMISE IMPACT

3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

Knowledge creation: Knowledge creation will be assured by collaboration between the leading experts on Cord Blood Banking, hiPSC generation and banking centres, Manufacturing centres, Clinicians, Regulatory Bodies and ethical experts for the entire process from clinical tissue banking, HLA- genetics, hiPSC technology and biobanking, to cell therapy product manufacturing. The Action will use this expertise to harmonise the available knowledge and data, and will initiate a common registry. The Action will act as a stakeholder platform by bringing together scientists, healthcare professionals and policy makers and will be able to create a common framework to identify and establish the necessary standardised technology to establish a safe and affordable hiPSC collection, suitable for the manufacture of therapeutic cell products. Standardisation is an essential goal of HAPLO- iPS.

Transfer of knowledge: Knowledge and expertise will be disseminated to stakeholders through open access peer-reviewed publications, meeting abstracts, presentations, workshops, websites and social media, regular workshops and conferences on key issues for the generation and delivery of hiPSC-based products. Networking will be stimulated in order to promote progress in the clinical translation of derivatives from hiPSC. Laboratory exchanges will be promoted through an exchange system to allow and motivate trainees to request support in training activities. Biotechnological companies involved in the Action will also contribute to the transfer of innovative knowledge acquired through the networking activities.

Career development: Training activities will constitute an important part of HAPLO-iPS. They will be aimed at creating interdisciplinary expertise while training a generation of young scientists and clinicians involved in cell therapy, who will acquire a set of new “enabling” skills and an inherently interdisciplinary approach to solve biological and bio-processing questions regarding hiPSC derived therapies. Specifically, young clinicians and researchers (particularly females and/or from ITC members) will have yearly the opportunity to make STSMs in reference Institutions and laboratories and attend Training Schools focused on the design, implementation and exploitation of ATMP. Therefore, The Action will be an excellent opportunity in a researcher or clinician career development regardless of their location, age or gender. Increasing the quality of their profile through leadership and interdisciplinary skills through specific training activities, this new knowledge will increase the success rate in complementary funding schemes such as ERC and MSCA. This active involvement will help to create new connections and joint

research proposals/ideas and learn from (senior) experts in the field while provide an opportunity for experience in international collaboration and management.

Impact for ITC countries will be maximised by the fact that:

- A significant percentage of the members are from ITC countries
- Several Key leadership positions in the Action Management are reserved to COST ITC.
- Training schools and STSMs specially focused on ITC young researchers and clinicians are established.
- Mentoring ITC young researchers will be provided through STM with renowned researchers and innovators from leading research and academic institutions and SMEs and will actively participate in COST Academy.
- ITC participants will have access to research facilities, scientific–technical infrastructures and sophisticated, state-of-the-art equipment.
- ITC participants participation in Widening actions under the Spreading Excellence and Widening Participation programme

3.2.2. PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

The HAPLO-iPS Action aims to establish a much-needed multidisciplinary network to successfully create a CB and hiPSC registry suitable for the manufacture of cell therapy products. The Action will develop a series of activities in order to promote collaboration between the participant teams to fill current knowledge gaps with breakthrough innovation. The Action plan will also take into account the need to create interdisciplinary expertise by training researchers with the potential to drive forward a new scientific community with specific activities focussed on young researchers' interest in the field. Multiple approaches will be considered to ensure maximum efficacy of the dissemination and exploitation activities of the Action, as described below (see WG6).

Dissemination Plan

Dissemination activities will mainly aim at promoting the new HAPLO-iPS technologies and guiding researchers towards their adoption well beyond the Action period Training schools for expert networking and mentoring for young researchers (e.g. hiPSC generation and characterisation, Immunology and Data handling) in order to disseminate knowledge among experts and young scientists in the field will be organised annually A complete training programme will be established. Proposed audience: young researchers)

- Working Group portal: The Working Group portal will efficiently deliver timely analysis of challenges, opportunities and solutions resulting from the Working Groups. The portal will facilitate community participation and engagement, communication and collaboration and documents sharing and management. This will enable an efficient coordination among members of the consortium and Working Groups. Proposed audience: researchers, patient associations and public in general))
- Website: The Development of the website will represent another communication tool to report on progress of the objectives of the Action to both scientists and the general public alike. It will be created to update the results and the outcomes of the Action as well as to keep a track on progress. The website will also be the portal to gain access to hiPSC and CB data and the registries. The website will be regularly updated.

- Social media activity: The Action main achievements will be disseminated and promoted through social media.(Proposed audience: researchers, patient associations and public in general))
- Presentations with the consensus documents and main achievements at network meetings (ISCBI, GAiT, ISCT, ISSCR, ISCI) and national and international conferences (IABS, ISCT, ISSCR, KSSCR, CSSCR, JSRM, Alliance of Asian Stem Cell Societies). (Proposed audience: researchers, ethic experts, regulatory bodies)
- Collaborations/Contributions to other EU stem cell and ATMP project meetings to promote interaction with initiatives related to the field. (Proposed audience: researchers, regulatory bodies, companies and cell therapy products manufacturers and clinical researchers).
- Manuscript preparation: a number of manuscripts (described in the WG activities) will be prepared for dissemination in relevant journals in the different areas of interest of this COST Action. (Proposed audience: researchers, regulatory bodies, companies and cell therapy products manufacturers and clinical researchers).

There will be a kick-off meeting at Action start and a final conference at the end. Regular WG meetings will be held throughout the Action to look at and deliver WG objectives and Annual meetings will be organised with all participants for WG reports and updates.

The Kick-off meeting will establish the final structure of the Working Groups and their tasks and the management of the Action. The final conference of the HAPLO-iPS Action will be organized at the end to discuss the final outcomes. Apart from the stakeholders involved in the Action, the scientific professionals from the participating countries and all experts from participating organizations will be invited to present and deliver the final outcomes of the Action.

Exploitation plans:

The COST Action will also ensure that the results of the Action, besides being widely disseminated, will also be utilized by transferring them into relevant research settings. The dissemination and exploitation activities of the Action will rely mostly on the solid and large networks of the partners. Throughout the Action, additional stakeholders will be added, and networking activities will be expanded if needed. The HAPLO-iPS Action aims to guide both researchers and physicians towards the implementation of the proposed solutions. The WG review and management meetings will review potential emerging Action IP and horizon scanning activity for disruptive technology.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORKPLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

Working Group number 1	1	**Start month**	1	**End month**	5
Work Group title	Sample selection				
Stakeholders involved	CB banks, hiPSC generators, immunologists				
Objectives **Source material screening, selection, collection and tracing** - Development of a common understanding of the /HLA / CB sample selection procedure - Coordination of information seeking tracing, collection and data curation of the selected samples					
Description of work **T.1.1** Review of initiatives and literature on generation on hiPSC generation from haplo-selected CB samples (coordination and communication opportunities to understand the diversity and commonalities of approaches in different centres/countries) and organize an immunology expert meeting for CB sample selection (involving experts in HLA and non-HLA rejection and tolerance mechanisms) **T.1.2** Contact (email, online conferences) CB EU banks for sample availability. **T.1.3** CB bank expert meeting to establish minimal HAPLO-iPS criteria for sample quality (identifying appropriate standards for starting materials), data and traceability					
Deliverables and milestones **D1.1:** Report on the common understanding of the haplo-selected CB samples selection procedure (M6). **D.1.2:** Report on the coordination of information seeking tracing, collection and data curation of the selected samples. (M15) **M1.1:** Decision on which CB samples need to be used for hiPSC generation and assess their availability.					

Working Group number	2	Start month	1	**End month**	2
Work Group title	hiPSC production				
Stakeholders involved	hiPSC generators, cell therapy products manufacturers				
Objectives **Generation and characterization of hiPSC** - Comparison and optimisation of methodologies for the generation of hiPSC suitable for the manufacture of therapeutic products					

Description of work **T.2.1** Literature review on reprogramming methodologies for hiPSC generation from haplo-selected CB samples and reprogramming and regulatory experts meeting selection of the most suitable method for reprogramming. **T.2.2** Literature review and consultation with expert networks on hiPSC characterisation criteria and reprogramming experts meeting selection of the hiPSC characterisation criteria **T.2.3** Literature review on production of hiPSC for manufacture of cell-based medicines and reprogramming experts meeting.
Deliverables and milestones **D2.1:** Report of existing reprogramming and characterisation methodologies for the selection of the most suitable method for hiPSC generation (M9) **D2.2:** SOP's for generation on hiPSC suitable for the manufacture of cell therapy products (M12) **M2.1:** Selection of the most suitable method for hiPSC generation from haplo-selected CB samples based on assessment of cell preparation/selection and reprogramming methods suitability for hiPSC- based medicinal products. **M2.2:** Selection of hiPSC characterisation criteria.

Working group number	3	Start month	15	End month	8
Work group title	Quality control, Biobanking and Registration of cell lines				
Stakeholders involved	hiPSCgenerators, celltherapyproductsmanufacturers, biobanks, regulatory bodies, hPSCreg				

Objectives

Quality control in hiPSC lines banking

- Identification of optimal systems for safety-assured and reliable cell therapies to promote standardisation of hiPSC scaling and banking for basic and clinical researchers and regulators.

Registry of hiPSC

- Development of a data resource and access platform and registry for available hiPSC lines suitable for the manufacture of therapeutic products based on the existing European human Pluripotent Stem Cell Registry (hPSCreg).

- Definition of hiPSC -associated data including origin, characterization and usage and linkage to existing repositories; provision of a source overview for donor material in CB via a single portal

- Establish core requirements for evaluation of suitability of hiPSC in terms of differentiation potential and elimination of reprogramming vectors.

- Standardisation of hiPSC characterisation for basic and clinical researchers and regulators.

Description of work T T.3.1 Literature review on quality control for hiPSC for the manufacture cell therapy products and meeting with product developers and regulators to identify recommended standards to be used for hiPSC production and biobanking. T.3.2 Workshop to review Task 3.1 output and agree quality, safety and standards guideline document including scientific, technological and regulatory challenges for Biobanking T.3.3 Registry implementation: literature review on international management of data, data standards and output involving data experts and map optimal route for stem data interoperability and registration. Incorporation into the hPSCreg.
Deliverables and milestones **D3.1:** Guidelines and standards road-map document and quality manual for hiPSC biobanking (M27). **D3.2**: Report of database for inclusion into European human Pluripotent Stem Cell Registry (hPSCreg). (M48). **M3.1:** Establish standards required for production and biobanking of hiPSC for the manufacture of products for cell therapy. M3.2: Selection of hiPSC line data to be collected.

Working Group number	4	Start month	27	End month	6
Work Group title	Safety and Regulation				
Stakeholders involved	Immunologists, regulatory bodies, cell therapy products manufacturers				

Objectives **Risk assessment** - Bring together expertise in genetic stability and tumorigenicity testing for evaluation of best current scientific practice in cell safety testing - Establishment of a consensus approach to identification and testing for the wider range of acute and emerging infectious diseases beyond the viral infections tested for in transplantation **Regulation** - Establishment of the regulatory landscape for donation and clinical use of CB-derived hiPSC and their derivatives.
Description of work **T.4.1** Literature review on safety issues (e.g., genetic instability, tumorigenicity, immune rejection) in the production on hiPSC for manufacture of cell therapy products. **T.4.2** Expert meeting on safety, regulatory and harmonisation issues

Deliverables and milestones
D4.1: Regulatory road-map document from donor samples to hiPSC production for the manufacture of cell therapy products (M36). **D4.2:** Guidelines for promoting quality and safety of hPSC-based medicines and cell therapy products (M39). **M4.1:** Identification of aspects where there is good EU and international harmonisation and remaining challenges for harmonisation. **M4.2:** Identify clinical risks and regulatory requirements for minimum best practice.

Working Group number	5	Start month	1	End month	7
Work Group title	Management, data handling and Ethics				
Stakeholders involved	Management team, CB banks, geneticists, experts in data handling and protection, ethical experts				

Objectives

Data handling:

- Establishment of a consensus in the management of data handling and protection

Ethics

- Establishment of ethical core documents for donation and clinical use of CB-derived hiPSC.

Description of work

T. 5.1 Management Group meeting for Working Group organisation

T.5.2 Experts meeting for data categorisation (e.g., Patent issues, licensing, know-how) and data confidentiality (donor personal data e.g., genetic sequence, donor treatment). Analysis of ethical, legal and social implications.

T.5.3 Literature review and experts meeting for agree on CB biobank Informed Consent templates and information provided for donors.

T.5.4 Experts meeting: review of CB registry and forward planning

Deliverables and milestones
D5.1: Report on the activity and management co-ordination and progress monitoring plan (M6). **D5.2:** Publication of guidelines for the management of data collection and protection (M30). **D5.3:** Proposal for HAPLO-iPS Consent Form and Information sheet to be signed by donors (M21). **M5.1:** Organisation of the Working Groups including identification of critical dependencies between Working Group objectives. **M5.2:** Consensus document for consent form and information sheet for donors following ethical criteria.

Working Group number	6	Start month	1	End month	8
Work Group title	Training and dissemination				
Stakeholders involved	CB banks, hiPSC generators, immunologists, experts in data handling, website developers, patient's organisations.				

Objective

Training

- Establishment of a training and exchange network for young researchers

Dissemination

- Diffusion of the Action by creating a website, social media activity and participation in meetings and international conferences.

Description of work

T.6.1 Training schools for expert networking and mentoring young researchers (e.g. hiPSC generation and characterisation, immunology and data handling) and direct lab exchanges

T.6.2 Portal and website development

T.6.3 Promotion of Social media activity

T.6.4 Presentations at network meetings (e.g., ISCBI, GAiT, ISCT, ISSCR) and international conferences (e.g., IABS, ISCT, ISSCR, KSSCR, CSSCR, JSRM, Alliance of Asian Stem Cell Societies). Collaborations/Contributions to other EU stem cell and ATMP Action meetings

T.6.5: Manuscript preparation

Deliverables and milestones

D6.1: Training programme and mentoring for young researchers and trainee reports on training exchanges (M15). **D6.2:** Report of portal development and of the launching of the website (M12). **D6.3:** Report of use of social media, presentations in meetings and collaborations with other initiatives (M48).

M6.1: Knowledge dissemination to experts and young scientists. **M6.2:** Dissemination of the Action through a website, social media and participation in meetings and EU projects in the stem cell and cell therapy field.

Working Group number	7	Start month	27	End month	8
Work Group title	Clinical application				
Stakeholders involved	regulatory bodies, cell therapy products manufacturers, clinical researchers, immunologists, hPSCreg, patient's organisations.				

Objectives

hiPSC-derivatives production

- Establishment and standardization of protocols for generate hiPSC-derivatives for cell therapy and their scaling.

Transplantation

- Establishment of safety and regulatory requirements for hiPSC-derivatives transplantation

- Establishment of transplantation protocols for hiPSC-derivatives therapy (including immunotherapy)

- Follow up of clinical trials

Description of work

T.7.1 Literature review on differentiation protocols for generate the most demanded hiPSC-derivatives for manufacture of cell-based medicines and cell manufacturers and regulatory experts meeting selection of the most suitable method for generate hiPSC-derivatives for cell therapy and their scaling. (Selection of SOP's)

T.7.2 Literature review on clinical trials with hiPSC-derivatives and cell therapy and cell manufacturers, clinical researchers, immunologists and regulatory experts meeting establishment of safety and regulatory requirements for cell therapy with hiPSC-derivatives.

T.7.3 Development of a data resource and access platform and registry for clinical trials with hiPSC-derivatives on the existing European human Pluripotent Stem Cell Registry (hPSCreg) and for the follow-up of clinical trials with hiPSC-derivatives on the existing European human Pluripotent Stem Cell Registry (hPSCreg)

Deliverables and milestones

D7.1: Standard Operating Procedure's for the recommended hiPSC differentiation protocols and their scaling. (M36). **D7.2:** Summary of safety, clinical and regulatory requirements for cell therapy with hiPSC-derivatives (M48). **D7.3:** Report on Database for inclusion of clinical trials and their follow-up in hPSCreg (M48**).**

M.7.1: Selection of the most suitable method for the manufacturing and scaling of hiPSC derivatives for cell therapy.

M.7.2: Evaluation of the safety and regulatory requirements for cell therapy with hiPSC-derivatives.

M.7.3: Evaluation of the clinical and immunological requirements for cell therapy with hiPSC-derivatives.

M.7.4: Provide a tool for Registry and Follow up of clinical trials with hiPSC-derivatives.

There will be a kick-off meeting at the initiation of the Action and a final conference at the end. Annual meetings will be organised with all participants for Working Group reports and updates. Working Groups will also hold meetings and workshops identified in the WG task descriptions and regular virtual planning and progress meetings.

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

All deliverables are described in the WG descriptions in section 4.1.1 and their timing is illustrated in the Gantt Chart in section 4.1.4.

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

The following table shows the risks of tasks together with the contingency plan associated:

Risk	**Contingency plan**
a) The Action could potentially develop intellectual property that might not be protected b) New disruptive technology (e.g., immune tolerance, tissue generation) could replace the need for a haplobank	a) This is highly unlikely to occur but meeting outputs would be held confidential until publication and the Management team would review all WG plans and emerging information and publications to assess risk to any potential IP and protect it appropriately. b) Horizon scanning for disruptive technology at experts meetings and WG review meetings
Companies decline to engage due to fear of revealing commercially sensitive information	Companies will not be expected to yield sensitive details of bioprocessing and characterisation.
a) If some CBU with a specific HLA-type will be not found b) CB samples found to be unsuitable for use	a) Other cord blood banks will be contacted or the next most frequent haplotype will be choose. b) Questionnaire enables selection of suitable samples for hiPSC and action plan to make samples suitable or seek further samples via international networks
If it is not possible to do face- to-face courses due to the impact of the Covid-19 pandemic	On-line courses will be organized
If new collaborations are not possible	HAPLO-iPS workshops developed to include and address issues of common interest with other projects.

4.1.4. GANTT DIAGRAM

Table 1. Gantt Diagram of HAPLO-iPS COST		Year 1				Year 2				Year 3				Year 4			
		T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
WG1. SAMPLE SELECTION						M1.1											
Task 1.1	Review of Initiatives and Literature on generation on hiPSC generation from haplo-selected CB samples and immunology expert meeting		D1.1														
Task 1.2	Contact CB EU banks for sample availability																
Task 1.3	CB bank expert meeting to establish minimal HAPLO-iPSC criteria for sample quality, data and traceability					D1.2											
WG2. hiPSC PRODUCTION					M2.1 M2.2												
Task 2.1	Literature Review on reprogramming methodologies for hiPSC generation from haplo-selected CB samples and reprogramming and regulatory experts meeting																
Task 2.2	Literature review and consultation with expert networks on hiPSC characterisation criteria and reprogramming experts meeting			D.2.1													
Task 2.3	Literature review on production of hiPSC for manufacture of cell-based medicines and reprogramming experts meeting				D.2.2												
WG3. QUALITY CONTROL, BIOBANKING, AND REGISTRATION OF CELL LINES										M3.1							M3.2
Task 3.1	Literature review on quality control for hiPSC for the manufacture cell therapy products and meeting with product developers and regulators																
Task 3.3	Workshop to agree quality, safety and standards guideline document									D3.1							
Task 3.4	Registry implementation																D3.2
WG4. SAFETY AND REGULATION													M4.1	M4.2			
Task 4.1	Literature review on safety issues in the production on hiPSC for manufacture of cell therapy products												D.4.1				
Task 4.2	Expert meeting on safety, regulatory and harmonisation issues													D.4.2			
WG5. MANAGEMENT, DATA HANDLING AND ETHICS			M5.1								M5.2						
Task 5.1	Management Group meeting for Working Group organisation		D5.1														
Task 5.2	Experts meeting for Data categorisation and Data confidentiality. Analysis of ethical, legal and social implications										D5.2						
Task 5.3	Literature review and experts meeting on Informed Consent templates and information provided for donors.							D5.3									
Task 5.4	Experts meeting: review of CB registry and forward planning																
WG6. TRAINING AND DISSEMINATION							M6.1		M6.2								
Task 6.1	Training schools for expert networking and mentoring young researchers and direct lab exchanges					D6.1											
Task 6.2	Portal and Website development				D6.2												
Task 6.3	Promotion of Social media activity																D6.3
Task 6.4	Presentations at network meetings and international conferences, Collaborations/Contributions to other EU stem cell and ATMP project meetings																
Task 6.5	Manuscript preparation																
WG7. CLINICAL APPLICATION													M7.1		M7.2	M7.3	M7.4
Task 7.1	Literature review on differentiation protocols for generate the most demanded hiPSC-derivatives												D7.1				
Task 7.2	Literature review on clinical trials with hiPSC-derivatives and cell therapy																D7.2
Task 7.3	Development of a data resource and access platform and registry for clinical trials and follow-up																D7.3
Meetings		WG Meeting MC Meeting				WG Meeting MC Meeting				WG Meeting MC Meeting				WG Meeting MC Meeting		Final conference	

References

1. Keeping kidneys. Bull World Health Organ. 2012;90(10):718-9.
2. Abranches E, et al. GMP Banking of Human Pluripotent Stem Cells: A US and UK perspective. Stem cell research. 2020;45:101805.
3. Álvarez-Palomo, B et al. Evaluation of the Spanish Population coverage of a prospective HLA haplobank of induced pluripotent stem cells. Stem Cell Research & Therapy. 2021; 12:233.
4. Bradley JA, et al. Stem cell medicine encounters the immune system. Nature reviews Immunology. 2002;2(11):859-71.
5. Giorgetti A, et al. Generation of induced pluripotent stem cells from human cord blood using OCT4 and SOX2. Cell stem cell. 2009;5(4):353-7.
6. Gourraud PA, et al. Standard methods for the management of immunogenetic data. Methods in molecular biology. 2012;882:197-213.
7. Jha BS, et al. Regulatory considerations for developing a phase I investigational new drug application for autologous induced pluripotent stem cells-based therapy product. Stem cells translational medicine. 2021;10(2):198-208.
8. Jo HY, et al. Development of genetic quality tests for good manufacturing practice-compliant induced pluripotent stem cells and their derivatives. Scientific reports. 2020;10(1):3939.
9. Kim JH, . Korea National Stem Cell Bank. Stem cell research. 2021;53:102270.
10. Kobold S, et al. A Manually Curated Database on Clinical Studies Involving Cell Products Derived from Human Pluripotent Stem Cells. Stem cell reports. 2020;15(2):546-55.
11. Lee S, et al. Repurposing the Cord Blood Bank for Haplobanking of HLA-Homozygous iPSCs and Their Usefulness to Multiple Populations. Stem cells. 2018;36(10):1552-66.
12. Liedtke S, et al. GMP-grade CD34(+) selection from HLA-homozygous licensed cord blood units and short-term expansion under European ATMP regulations. Vox Sang. 2021;116(1):123-35.
13. Nakatsuji N, et al. HLA-haplotype banking and iPS cells. Nature biotechnology. 2008;26(7):739-40.
14. O'Shea O, et al. Development and implementation of large-scale quality control for the European bank for induced Pluripotent Stem Cells. Stem cell research. 2020;45:101773.
15. Okita K, et al. Immunogenicity of induced pluripotent stem cells. Circulation research. 2011;109(7):720-1.
16. Petrus-Reurer S, et al. Generation of Retinal Pigment Epithelial Cells Derived from Human Embryonic Stem Cells Lacking Human Leukocyte Antigen Class I and II. Stem cell reports. 2020;14(4):648-62.
17. Rim YA, et al. Recent progress of national banking project on homozygous HLA-typed induced pluripotent stem cells in South Korea. J Tissue Eng Regen Med. 2018;12(3):e1531-e6.
18. Saidi RF, et al. Challenges of organ shortage for transplantation: solutions and opportunities. Int J Organ Transplant Med. 2014;5(3):87-96.
19. Sullivan S, et al. Quality control guidelines for clinical-grade human induced pluripotent stem cell lines. Regenerative medicine. 2018;13(7):859-66.
20. Suzuki D, et al. iPSC-Derived Platelets Depleted of HLA Class I Are Inert to Anti-HLA Class I and Natural Killer Cell Immunity. Stem cell reports. 2020;14(1):49-59.
21. Takahashi K, et al. Induction of pluripotent stem cells from fibroblast cultures. Nature protocols. 2007;2(12):3081-9.
22. Taylor CJ, et al. Banking on human embryonic stem cells: estimating the number of donor cell lines needed for HLA matching. Lancet. 2005;366(9502):2019-25.
23. Taylor CJ, et al.. Generating an iPSC bank for HLA-matched tissue transplantation based on known donor and recipient HLA types. Cell stem cell. 2012;11(2):147-52.

24. Xu H, et al. Targeted Disruption of HLA Genes via CRISPR-Cas9 Generates iPSCs with Enhanced Immune Compatibility. Cell stem cell. 2019;24(4):566-78 e7.
25. Yu J, et al. Induced pluripotent stem cell lines derived from human somatic cells. Science. 2007; 318(5858): 1917-20.